The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JON A. WEIDANZ, KIMBERLY F. CARD and HING C. WONG

Appeal No. 2006-0334
Application No. 08/813,781

HEARD: February 9, 2006

Before ELLIS, MILLS, and GRIMES, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72, which are all of the claims on appeal in this application. Claims 3, 9, 13, 15, 21-60, 62-64, 66 and 68 have been withdrawn from consideration by the examiner.

Claim 1 is representative and reads as follows:

1. A soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor comprising an antigen binding pocket, wherein the single-chain T cell receptor comprises a V-α region covalently linked to a V-β region by a peptide linker sequence that effectively positions the V-α region and the V-β region to form the antigen binding pocket, the soluble fusion protein further comprising a C-β region fragment.

The prior art references cited by the examiner are:

Barbas 5,759,817 June 2, 1998

Chung et al. (Chung), "Functional three-domain single-chain T-cell receptors," Proc. Natl. Acad. Sci, USA, Vol. 91, pp. 12654-12658 (1994)

Onda et al., (Onda), "A phage display system for detection of T cell receptor-antigen interactions," Molecular Immunology, Vol. 32, No. 17/18, pp. 1387-1397 (1995)

Huse et al., (Huse), "Application of a filamentous phage pVIII fusion protein system suitable for efficient production, screening, and mutagenesis of F(ab) antibody fragments," Journal of Immunology, Vol. 149, No. 12, pp. 3914-3920 (1992)

Grounds of Rejection

Claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72 stand rejected under 35 U.S.C. §103(a) over Chung in view of Barbas, Onda and Huse.

We affirm this rejection.

Claim Grouping

According to appellants, "[a]ll of claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72 stand or fall together for the purpose of the present appeal." Brief, page 2. Therefore, we select claim 1 as representative of the claims on appeal. 37 C.F.R. § 1.192(c)(7), now 37 C.F.R. § 41.37(c)(1)(vii) (2004).

DISCUSSION

Background

Appellants summarize their invention (Brief, pages 1-2) as follows:

> The claimed invention features a soluble fusion protein engineered to include a bacteriophage coat protein fused to a single-chain T cell receptor ("scTCR"). The single-chain T cell receptor was itself designed to include an alpha-variable region ("V-α") fused to a beta variable region ("V-β"). The single-chain T cell receptor forms a pocket that binds antigen when the antigen [sic]. The claimed soluble fusion protein further includes a beta-constant region ("C-β") region that can be fused to V-β, for example.
>
> T cells help defend the body against infection. The cells have membrane bound receptors that bind foreign antigen with the assistance of a protein complex called "MHC". A key receptor is called the T cell receptor ("TCR"). The chemical structure and function of the TCR has been extensively studied. For instance, it is known that formation of a TCR-antigen-MHC complex is an important step toward fighting infection.
>
> Appellants discovered that by adding a bacteriophage coat protein to the scTCR, it is possible to produce a fully soluble and functional scTCR. Unlike prior scTCRs, the claimed fusion proteins were found to be fully soluble, functional, and obtainable in significant quantities without difficulty.

Obviousness

Claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72 stand rejected under 35 U.S.C. §103(a) for obviousness over Chung in view of Barbas, Onda and Huse.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings from the prior art would have suggested the claimed

subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). An obviousness analysis requires that the prior art both suggest the claimed subject matter and provide a reasonable expectation of success to one reasonably skilled in the art. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). With this as background, we analyze the prior art applied by the examiner in the rejection of the claims on appeal.

As evidence of obviousness in support of the rejection the examiner relies on Chung, Barbas, Onda and Huse. The examiner argues (Answer, page 4)

> Chung et al. teach[ ] a single chain T cell receptor which specifically binds to peptide ligand (see abstract). Chung et al. further teach[ ] one embodiment of human single chain TcR in which C-terminus of Vα domain is linked to N-terminus of Vβ chain via a 15 amino acid residue flexible amino acid linker and the C-terminus of the Vβ chain is linked to the beta chain constant domain (see Figure 1). ... Chung et al. teach that the TcR fusion protein can bind antigenic protein, thus teaching that the TcR fusion protein comprises an antigen binding pocket. Chung et al. teach[ ] a TcR fusion protein comprising Vα-peptide linker-Vβ-Cβ linked to GPI anchor and expression of such a fusion protein in a transfected eukaryotic cell (see results section). Chung et al. disclose that the soluble form of TcR protein could be readily obtained by enzymatic cleavage with phosphatidylinostol-specific [sic] phospholipase C (PI-PLC) (see page 12656). ... Chung et al. further teach that TcR fusion proteins which do not contain the Cβ do not fold into the native conformation. The scTCR disclosed by Chung et al. meet the length limitations of the Vα and Vβ region recited in claims 69 and 71. Chung et al. teach a soluble fusion protein comprising a Vα peptide linker-Vβ-Cβ fragment-protein tag (eg. GPI).

The examiner acknowledges that Chung does not teach a TCR fusion protein further comprising bacteriophage VIII coat protein. Answer, page 5. To make up for this deficiency the examiner relies on Barbas. Id.

According to the examiner (Id., page 5)

> Barbas discloses a soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a single-chain heterodimeric receptor (see column 2, third paragraph, single chain antibody). ... Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable (V) and constant region and T cell receptor has similarities in genetic organization and function to immunoglobulins (see column 19, lines 19-22, in particular). ... Barbas discloses that expression vectors expressing soluble fusion proteins in which the ligand binding region is fused to bacteria coat protein allows the expression of the multiple fusion proteins on the surface of phage particles .... (see column 39 line 64 through column 40, line 7, in particular). Barbas further discloses that a short length of amino acid sequence at the amino end of a protein (IE a protein tag) directs the protein to periplasmic space (see column 8, lines 49-55, in particular).

Onda is relied on for its disclosure of "a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a construct of a single-chain of the T cell receptor by a peptide linker sequence wherein the single TcR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular). Onda et al. also teach that TcR-bacteriophage coat protein fusion protein can be used to study specific binding interactions of the TcR chain to antigenic ligands (see paragraph bridging pages 1394-1395, in particular)." Answer, page 6.

Huse teaches (Id.)

> that fusion proteins comprising a fusion protein comprising Fab fragment of immunoglobulin (which comprises the antigen binding pocket of the immunoglobulin molecule) and bacteriophage VIII coat protein can be produced and display the fusion protein when expressed in a M13 derived vector. Huse et al. further teach that bacteriophage VIII coat protein fusion protein can [be] recovered from culture medium or from the periplasmic space.

The examiner concludes (Answer, pages 6-7)

> it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a soluble TcR fusion protein comprising the Vα-peptide linker-Vβ-Cβ fragment-protein taught by Chung et al. linked to a bacteriophage VIII coat protein because Barbas et al. and Onda et al, teach TcR-bacteriophage VIII coat fusion proteins can be used to study antigen binding properties of such a fusion protein and Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria and recovered in relatively large quantities. One with skill in the art would be motivated to make such a fusion protein to study the antigen binding region of the TcR component or to use the protein to elicit anti-idiotypic antibodies. One with skill in the art would be motivated to make such a fusion protein in which the Vα and Vβ region was derived from human TcR in order to study human TCR properties or to elicit anti-idiotypic antibodies to the TcR component of the protein.

We find on the record and evidence before us, that the examiner has made out a prima facie case of obviousness.

In particular, Chung teaches that a single chain TCR linked to a GPI signal domain provides for stable expression of the scTCR on the surface of E. coli. The scTCR (having Vα, Vβ, and Cβ regions) of the receptor exhibited proper folding and was obtained in soluble form after enzymatic cleavage. Page 12654, column 2. Chung goes so far as to suggest that the "sc design may allow the construction of TCR phage display libraries similar to those made with sc antibodies." Page 12658, column 1. Barbas linked bacteriophage coat proteins to heterodimeric immunoglobulin ligand binding regions and taught that other members of the family of antigen binding molecules such as the T cell receptor found on the surface of T-cells could be used. See, e.g., col. 19, lines 7-28. Thus, Barbas discloses a method of making "a phage

display library of DNA molecules capable of expressing a fusion protein on the surface of a filamentous phage particle," (col. 1, lines 18-21) using immunoglobulins and suggests doing the same with the TCR. Onda linked bacteriophage coat protein to an even smaller portion of the T-cell receptor, the Vα region only, and was able to express a soluble TCRα on the phage surface in E. coli. Given the teachings of Chung with respect to the construction of soluble scTCR having the Vα, Vβ, and Cβ domains which can be expressed in a properly folded form on cell membrane, and the express suggestion to construct TCR phage display libraries using said domains of the TCR, one of ordinary skill in the art would have been motivated to express a soluble fusion protein comprising a single chain TCR having the Vα, Vβ, and Cβ regions covalently linked to a bacteriophage coat protein. Such person would have had a reasonable expectation of success because both larger single chain immunoglobulin receptor molecules and Fab portions thereof, in the form of bacteriophage coat protein fusion proteins (Barbas and Huse), and a smaller portion of the TCR, the Vα region of TCR only, in the form of bacteriophage coat protein fusion proteins (Onda), were found to be soluble when expressed in E. coli.

Where the prior art, as here, gives reason or motivation to make the claimed invention such as for the construction of TCR phage display libraries which allow for the simultaneous cloning and screening of molecules that bind to the T-cell receptor, the burden then falls on appellants to rebut that prima facie case. Such rebuttal or argument can consist of any other argument or presentation of evidence that is

pertinent. In re Dillon, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991).

In rebuttal appellants argue, "[u]nlike the TCR, the scTCR binds antigen with only one chain. The TCR and scTCR are structurally distinct proteins that are different molecules that bind antigen in different ways. Compare Exhibit A (i)-(ii) (showing eg., substantial structural differences between a TCR and scTCR)." Brief, page 8. Appellants further argue, there is "no teaching or suggestion in the cited prior art that Chung's anchor molecules could be substituted with Barbas' bacteriophage coat proteins." Brief, page 18. "The anchor molecules are entirely different from the coat proteins of Barbas both in terms of chemical structure and function. For example, Chung's anchors are hydrophobic cell membrane proteins while those of Barbas are relatively more hydrophilic bacteriophage coat components." Id. Thus, appellants contend that "[t]he obviousness rejection falls far short of establishing any nexus between Chung's anchors, which are attached to his scTCRs, and the coat proteins reported by Barbas." Id.

We are not persuaded by this argument. Chung explicitly suggests the scTCR may be used in a phage display library. Barbas describes bacteriophage coat protein fusion proteins for use in phage display and states (col. 2, lines 8-13) that "cpVIII has been extensively studied as a model membrane protein because it can integrate into lipid bilayers such as the cell membrane." Barbas (col. 2, lines 23-32) further states that "cpIII includes a stretch of hydrophobic amino acids responsible for a membrane

anchor function." The pending claims do not require a specific bacteriophage coat protein. In our view, Barbas provides a basis to construct a fusion protein comprising a well known bacteriophage coat protein, such as cpVIII, and a single chain TCR as suggested by Chung.

While appellants argue that TCR and scTCR bind antigen differently, appellants do not indicate how these differences in structure and antigen binding would affect their ability to be expressed when linked to a bacteriophage coat protein in the form of a fusion protein. Nor do appellants consider these differences in view of Chung's successful expression of soluble scTCR and in view of the varied structures and sizes of immunogloblulin and receptor fusion proteins successfully expressed in Barbas, and other of the cited references.

Appellants argue, "Onda does not disclose a TCR or scTCR fusion to bacteriophage coat protein as alleged by the Examiner in the August 25, 2000 and June 17, 2002 Office Actions. Instead, Onda reports fusion of TCR α chains to bacteriophage coat protein. ... These constructs are significantly smaller (and less likely to cause solubility problems when fused to coat proteins) than the scTCR fusions Appellants successfully made."[1] Brief, page 14. "Moreover, the Examiner ignored Onda's clear hesitation about reading too much from TCR α chain constructs that

[1] We note however the prior art evidences significantly larger molecules such as soluble heterodimeric immunoglobulins, ligand binding portions of immunoglobulins and even Fab fragments of antibodies were successfully expressed on bacteriophage coat proteins.

include a fused bacteriophage coat protein. According to Onda, the interactions of the constructs were unusual and not typical of TCR-ligand interactions. See above and Onda at pg. 1395, col. 1." Id.

We are not persuaded by this argument. Onda indicated that a fusion protein comprising only the Vα region of the TCR was able to bind peptide antigens was unexpected. However, the fact that the fusion protein was able to bind indicates that one skilled in the art had a reasonable expectation of success, as evidenced by Chung, that an scTCR protein having three domains, Vα, Vβ, and Cβ, would bind antigens when fused to a bacteriophage coat protein (cpVIII). Appellants do not indicate, with appropriate evidence, why one of ordinary skill in the art would not have been able to express soluble receptor molecules (such as scTCR) on the surface of bacteriophage, especially in view of the teachings of Barbas that larger immunoglobulin receptor molecules can be covalently linked to bacteriophage coat protein and properly form an antigen binding pocket on the phage surface. Moreover, Chung evidences the proper folding of scTCR having Vα, Vβ, and Cβ regions (similar to that claimed), albeit in a different fusion protein, further intimating a likelihood of success of obtaining a properly folded, functional scTCR in the form of a fusion protein.

Regarding Huse, appellants argue "Huse reported difficulties producing some bacteriophage coat protein fusions[.]" Brief, page 15.

> The Huse reference ... reported that not all F(ab)-pVIII (bacteriophage) coat proteins could be made at high titre. That is, Huse stated that the bacteriophage may not tolerate some amounts of F(ab) constructs, thereby decreasing phage titres and overall F(ab) yield. See above and

> Huse at pg. 3919, col. 2. When Huse is read in its entirety, as it should, the Examiner's statement that "Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria" is an unsupported generalization. Huse clearly found that some amounts of heterodimeric F(ab) constructs harmed the bacteriophage that carried them. In view of this warning, a worker in the field would have good reason to doubt whether a bacteriophage could be fused to a scTCR or even a heterodimer such as a TCR without considerable experimentation.

Brief, pages 15-16. This argument does not address a limitation in the claims. The claims do not require any specific phage titer. Huse evidences that while not all F(ab) constructs linked to a bacteriophage could be made in high titre, they still could be made.

In conclusion, we are not persuaded by appellants' arguments. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." In re Merck & Co., Inc., 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986). The test of obviousness is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). For the reasons discussed in detail above, we conclude that the combined teachings of the cited references support a prima facie case of obviousness established by the examiner which remains unrebutted by appellants.

CONCLUSION

Therefore, the rejection of claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72 under 35 U.S.C. §103(a) over Chung in view of Barbas, Onda and Huse is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

JOAN ELLIS
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

ERIC GRIMES
Administrative Patent Judge

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